

or organism comprising a nucleotide sequence encoding a Gas1 protein or a functional equivalent, derivative or bioprecursor thereof, which is capable of inducing apoptosis in said cell, and ii) a further sequence encoding a protein which is otherwise lethal to said cell in itself or in response to a lethal stimulus in the presence of Gas1;

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- (b) inhibiting function and/or expression of said Gas1 protein or functional equivalent, derivative or bioprecursor thereof or a protein in the apoptotic pathway of which Gas1 is a component;
- (c) expressing said sequence encoding said otherwise lethal protein;
- (d) contacting said cell with a compound to be tested; and
- (e) monitoring the effect of said compound on said otherwise lethal protein compared to an identical cell which has not been contacted with said compound.

REMARKS

Claims 1-5, 7-9, 11, 14-17, 22, 28, 29, 31, 32, 34, 36-38, 40, 42, 43, 45, 48-52 have been amended for U.S. patent practice. Claims 19-21, 46 and 47 have been canceled and claim 54 has been added as a rewrite of claim 20. Applicants submit a sequence listing along with a Computer Readable Form of the Sequence Listing. The undersigned hereby states that the Paper Copy and the Computer Readable Form are identical. The copy of the patent application included with this filing has been amended to introduce SEQ ID NOS for the oligonucleotides. No new matter has been added by

these amendments. Favorable consideration of this application is respectfully requested.

Respectfully submitted,

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Version to Show Changes Made

The specification has been amended to add the following paragraph after the title of the application:

--This application is a national stage application of PCT/EP00/08182 filed August 21, 2000 entitled "Gas 1 Polypeptides" which claims priority from EP 99306702.4 entitled "Gas1 Polypeptides" filed August 24, 1999, the contents of these applications is incorporated by referenced into this application.--

The claims have been amended as follows:

1. (Amended) A method of inhibiting the lethal effect of expressing an otherwise lethal protein in a cell, said method comprising the steps of:

- (a) providing a cell, tissue or organism having (i) a nucleotide sequence encoding a Gas1 protein, or a functional equivalent, derivative or bioprecursor thereof, which is capable of inducing apoptosis in said cell and (ii) a further nucleotide sequence encoding a protein which is otherwise lethal to said cell in itself or in response to a lethal stimulus in the presence of Gas1;
- (b) inhibiting function and/or expression of said Gas1 protein or functional equivalent, derivative or bioprecursor thereof; and
- (c) expressing said sequence encoding said otherwise lethal protein

wherein said protein normally induces the expression or activates either Gas1 protein or a protein in the signal transduction pathway of which Gas1 is a component.

2. (Amended) A method of identifying compounds which inhibit or enhance expression or activity of proteins which are lethal to a cell, tissue or organism said method comprising the steps of:

- (a) providing a cell, tissue or organism comprising a nucleotide sequence encoding a Gas1 protein or a functional equivalent, derivative or bioprecursor thereof, which is capable of inducing apoptosis in said cell, and ii) a further sequence encoding a protein which is otherwise lethal to said cell in

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itself or in response to a lethal stimulus in the presence of Gas1;

(b) inhibiting function and/or expression of said Gas1 protein or functional equivalent, derivative or bioprecursor thereof or a protein in the apoptotic pathway of which Gas1 is a component;

(c) expressing said sequence encoding said otherwise lethal protein;

(d) contacting said cell with a compound to be tested; and

(d) monitoring the effect of said compound on said otherwise lethal protein compared to an identical cell which has not been contacted with said compound

wherein said proteins normally induce the expression or activate either the Gas1 protein or a protein in the signal transduction pathway of which Gas1 is a component.

3. (Amended) A method according to claim [1 or] 2 wherein said expression or activity of Gas1 protein is inhibited by providing a nucleic acid molecule in said cell which is capable of hybridising to mRNA corresponding to Gas1 DNA to prevent expression thereof.

4. (Amended) A method according to claim [1 or] 2 wherein said expression or activity of said Gas1 protein is inhibited by inhibiting the expression or activity of a protein in the pathway of which Gas1 is a component.

5. (Amended) A method according to [any of] claim[s] [1 to 4] 2 wherein said cell is induced to express said Gas1 protein by contacting said cell with a stimulus that increases intracellular calcium levels in said cell.

7. (Amended) A method according to [any of] claim[s] [1 to 6] 2 wherein said further sequence encoding said otherwise lethal protein is expressed by providing it on a suitable expression vector.

8. (Amended) A method according to [any of] claim[s] [1 to 7] 2 wherein said lethal protein is a highly expressed recombinant protein.

9. (Amended) A method according to [any of] claim[s] 1 to 7] 2 wherein said otherwise lethal protein comprises any of a glutamate, NMDA, AMPA or kainate receptor.

11. (Amended) A method according to [any of] claim[s] 3 [to 9] wherein said nucleic acid molecule is provided as an oligonucleotide or as a vector including a nucleotide sequence of said nucleic acid molecule.

14. (Amended) A method according to [any of] claim[s] [1 to 13] 2 wherein said Gas1 protein is of mammalian origin.

16. (Amended) A method according to claim 14 [or 15] wherein said Gas1 protein comprises the amino acid sequence depicted in either of Sequence ID No. 2 or 4 or a functional equivalent, derivative or bioprecursor thereof.

17. (Amended) A compound identifiable as an inhibitor or an enhancer of expression or activity of an otherwise lethal protein according to the method[s of any] of claim[s] 2 [to 15].

22. (Amended) The method of claim 54 [Use according to claim 20 or 21] wherein said cell is associated with a disease condition selected from the group consisting of [comprises any of] a neurological disorder, a cardiovascular disorder, an autoimmune disorder, a neuroendocrine disorder or cancer.

26. (Amended) A nucleic acid molecule according to claim [24 or] 25 which is a DNA sequence.

28. (Amended) A nucleic acid molecule according to claim [24,] 26 [or 27] comprising the sequence of nucleotides according to Sequence ID No. 1.

29. (Amended) An antisense molecule capable of hybridising to the nucleic acid molecule of [any of] claim[s] [24 to 28] 25 under conditions of high stringency.

31. (Amended) A [Gas1] protein encoded by [a] the nucleic acid molecule of Sequence ID NO. 1 or a nucleic acid molecule capable of hybridizing to Sequence ID NO. 1 or its complement under conditions of high stringency [according to any of claims 24 to 28].

32. (Amended) A [Gas1] protein comprising the [an] amino acid sequence illustrated in Sequence ID No. 2.

34. (Amended) An expression vector comprising a nucleic acid molecule according to [any of] claim[s] 25 [24 to 28] or a nucleic acid molecule capable of hybridizing to Sequence ID No.1 under conditions of high stringency.

36. (Amended) An expression vector according to claim 34 [or 35] comprising a tissue or cell specific promoter.

37. (Amended) An expression vector according to [any of] claim[s] 34 [to 36] further comprising a sequence encoding a proapoptotic protein.

38. (Amended) An expression vector according to [any of] claim[s] 34 [to 37] which is inducible for expression of [said Gas1 polypeptide] a protein comprising the amino acid sequence of Sequence ID No.2 or [said] a polypeptide capable of inducing apoptosis in a cell.

40. (Amended) A host cell, tissue or organism, transformed, transfected or infected with a vector according to [any of] claim[s] 34 [to 39].

42. (Amended) A method according to claim 41 wherein said cell in step (a) comprises a [cell according to claim 40] host cell, tissue or organism transformed, transfected or infected with a vector comprising a nucleic acid molecule encoding a protein capable of inducing apoptosis in a cell comprising an amino acid sequence according to Sequence ID No. 4 [according to any of claims 24 to 28] or a nucleic acid molecule capable of hybridizing to Sequence ID No.1 under conditions of high stringency.

43. (Amended) A compound identifiable as an inhibitor or an accelerator of cell death according to the method of claim [41 or] 42.

45. (Amended) A pharmaceutical composition comprising any of a nucleic acid molecule encoding a protein according to Sequence ID No. 4 or a nucleic acid molecule capable of

stringennt hybridization thereto; [according to any of claims 24 to 28,] an antisense molecule capable of hybridizing to a nucleic acid molecule encoding a protein according to Sequence ID No. 4 under conditions of high stringency; [according to claim 29 or 30,] or a protein encoded by a nucleic acid molecule capable of hybridizing to Sequence ID No. 1 under stringent hybridization conditions [according to any of claims 31 to 33] together with a pharmaceutically acceptable carrier, diluent or excipient therefor.

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48. (Amended) The method of [Use according to] claim [47] 22, wherein said neurological disorder is any of, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, a neurological condition caused by thrombosis or cerebral trauma.

49. (Amended) The method of [Use according to] claim [47] 22, where said cardiovascular disorder is a heart attack.

50. (Amended) The method of [Use according to] claim [47] 22, wherein said autoimmune disorder is multiple sclerosis.

51. (Amended) The method of [Use according to] claim [47] 22, wherein said neuroendocrine disorder is necrosis of the pituitary gland.

52. (Amended) An antibody capable of binding to a protein comprising an amino acid sequence according to Sequence ID NO.2 or Sequence ID No. 4 [according to any of claims 31 to 33].

Claim 54 has been added:

54. A method for decreasing the expression of a protein that is lethal to a cell, wherein the protein normally induces the expression or activation of either the Gas1 protein or a protein in the signal transduction pathway of which Gas1 is a component comprising the step of: contacting the cell with a therapeutically effective dose of a compound identified by (a) providing a cell, tissue or organism comprising a nucleotide sequence encoding a Gas1 protein or a functional equivalent, derivative or bioprecursor thereof, which is capable of inducing apoptosis in said cell, and ii) a further sequence encoding a protein which is otherwise lethal to said cell in itself or in response to a lethal stimulus in the presence of Gas1; (b) inhibiting function and/or expression of said Gas1 protein or functional equivalent, derivative or bioprecursor thereof or a protein in the apoptotic pathway of which Gas1 is a component;

- (c) expressing said sequence encoding said otherwise lethal protein;
- (d) contacting said cell with a compound to be tested; and
- (e) monitoring the effect of said compound on said otherwise lethal protein compared to an identical cell which has not been contacted with said compound.